1. Detailed Action

2. The objection to claims 4-23 are withdrawn in light of applicant's amendment filed 7/23/2008.

3. (modified rejections)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 28-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula I with, a equal to 1, or 2, and b equal to 1 or 2, R1 equal to halogen, R2 equal to halogen or C1-6 alkoxy, R3 equal to an optionally substituted N-linked heterocycle which is piperidine or morpholinyl, does not reasonably provide enablement for using the compounds of formula I with a, b, R1, R2, and R3 equal to moieties other than those stated above. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is

"undue". These factors include 1)the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

a) Determining if any particular claimed compounds with a, b, R1, R2, and R3 equal to moieties other than those stated to be enabled above, would be active would require synthesis of the substrate and subjecting it to testing with pharmacological assays. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found at pages 18-28, which merely states Applicants' intent to make and use such compounds. c) In the instant case none of the working examples contains any radicals a, b, R1, R2, and R3 equal to moieties other than those stated to be enabled above.

d) The nature of the invention is treatment of human diseases with Applicants' compounds. This involves physiological activity e) There is no reasonable basis for the assumption that the myriad of compounds embraced by the present formula (I) will all share the same biological

properties. The diverse claimed compounds are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I). Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the

specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

(new rejections)

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 44-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an

enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Determining if any particular claimed compound would treat anxiety or depression would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating depression and anxiety is found at page 11, lines 20-40 which merely states Applicants' intention to do so. Applicants describe formulations at page 11, lines 1-18. Doses required to practice their invention are described at page 13, lines 9-17. A 20,000-fold range of doses is recommended. Since these compounds have never been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are no assays provided

which are correlated to the treatment of anxiety or depression. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of depression and anxiety with the instant compounds, which involves physiological activity. e) The state of the clinical arts is that 5-HT2C receptors are predominantly localised in the brain and their dysregulation may contribute to particular symptoms of anxiety and depression. See the Abstract of Jenck et. al. 5-HT2C receptor antagonists such as SB-2006 46 A or SB-221284 show signs of anxiolytic – like activity in tests for conditioned and phobic-like anxiety in rodents whereas they are inactive in tests indicative of antidepressant, antiOCD and antipanic activity. These results are consistent with an important hypthesis proposing that 5-HT has a complex, dual action on the neural mechanism of anxiety by either facilitating or inhibiting different kinds of anxiety in different brain regions. See Abstract, page 1587, of Jenck et. al.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166

USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

MPEP §2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is

clearly justified here and undue experimentation will be required to practice Applicants' invention.

(Response to Applicant's Arguments)

The applicant traverses the examiner's enablement rejection arguing that the fact that experimentation may be complex, does not make it undue - the applicant then goes on say that the specification provides a number of synthetic procedures which would enable one of ordinary skill in the art to prepare the compounds of this invention. However, these procedures do not enable one of ordinary skill in the art to use these various compounds to in the treatment of various CNS disorders. The applicant does not disclose any working examples of any compounds used to treat any of the claimed diseases - nor does the applicant disclose any pharmacological experimental data or biological assays regarding the compounds. Therefore, undue experimentation would be required to synthesize and test, compounds that are dissimilar in chemical properties, due to nonobvious structures.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 1625

/Binta M Robinson/
Examiner, Art Unit 1625
BMR
October 21, 2008